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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,749	11/29/2001	Gerritdina Hendrika Van Geel-Schutten	BO43388-CIP	3543

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,749	VAN GEEL-SCHUTTEN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date. _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-6-04 has been entered.

Claims 29-48 are now at issue and are present for examination.

Applicants' amendments and arguments filed on 2-6-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a glycosyltransferase enzyme comprising amino acids 531-1781 of SEQ ID NO:2 or amino acids 972-1781 or amino acids 972-1514 of SEQ ID NO:2 or comprising an amino acid sequence that has at least 95%, 96%, 97% homology to amino acids 531-1781 of SEQ ID NO:2 or amino acids 972-1781 of SEQ ID NO:2 or at least 98%

amino acid homology to amino acids 972-1514 of SEQ ID NO:2 that is isolated from L.reuteri, and wherein said enzyme produces a glucan having 38%-48% 4-linkedanyhydroglucose units, 17-28% 6-linked anhydroglucoase units and 7-20% 4,6,-linked anhydroglucose units in the presence of sucrose does not reasonably provide enablement to any such glycosyltransferase comprising fragments 100 or 200 amino acids that exhibit even 98% homology to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 30, 32-33 are so broad as to encompass any glycosyltransferase from any source that comprises fragments 100 or 200 amino acids that exhibit even 98% homology to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glucosyl transferases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be

tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one glucosyltransferase. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 and its specific fragments)see above) as a glucosyltransferase but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any glycosyltransferase comprising short fragments of SEQ ID NO:2 (such as 100 or 200 amino acids) that are at least 98% identical to fragments of specific amino acids such as 531-1781, 972-1514 or 1515-1781, of SEQ ID NO:2. including variants, mutants and recombinants because the specification does not establish: (A) regions of the protein structure which may be modified without effecting its activity; (B) the general tolerance of glucosyl transferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues in any glycosyltransferase or its specific fragments with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including glucosyl transferases with an enormous number of amino acid modifications of the glycosyltransferase of SEQ ID NOS: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of glucosyl transferases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection arguing at length that preferred methods to determine identity are designed to give largest match between the sequences tested and methods to determine identity and similarity are codified in publicly available computer programs which are available to the public. Applicant lists several of the available computer programs. Applicant also argues at length regarding how those skilled in the art can determine the amino acid similarity taking into account the so-called conservative amino acid substitution and therefore, believes that claims are supported. Examiner respectfully disagrees with such an argument as being persuasive to overcome the instant rejection because while such methods are well known to the skilled artisan, producing variants as claimed by applicants requires that one of ordinary skill in the art, to know or be provided with guidance regarding specific amino acid residues that can be modified without affecting the activity of the enzyme as well as for the selection of which of the infinite number of variants have the claimed property (i.e., both structure and function). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, (i.e., polypeptides comprising any of 100 to 200 amino acids of specific fragments of SEQ ID NO:2 or parts of the same) the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting activity; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a

rational and predictable scheme for modifying any amino acid residue on the polypeptide or specific parts of the polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29-36, 38-44, 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by van Geel-Schutten et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703). This rejection is based upon the public availability of a printed publication. Claims 29-36, 38-44, 46-48 of the instant application are drawn to an isolated protein having glycosyltransferase activity and whose amino acid sequence is either identical to SEQ ID NO:2, or comprises fragments that are homologous to certain specific fragments of SEQ ID NO:2 are changed and wherein said enzyme can produce a glucan having 38-48% 4-linked anhydroglucose units, 17-28% 6-linked anhydroglucose units and 7-20% 4,6-linked anhydroglucose units using sucrose. van Geel-Schutten et al. disclose a glycosyltransferase also known as glucansucrase isolated from *L.reuteri*. Since the enzyme is isolated from the same microorganism that is claimed by the applicants, Examiner takes the position that the enzyme disclosed in the reference and the enzyme disclosed in the instant application are the same even though the reference does not

disclose the amino acid sequence. Examiner also takes the position that amino acid sequence information is inherent to the proteins/enzymes and therefore the enzyme in the reference has the same amino acid sequence information as that disclosed by the applicants. Thus van Geel-Schutten et al. anticipate claims 29-36, 38-44, 46-48 of this application as written.

In response to the previous Office action, applicants have traversed the above rejection arguing that the above reference fails to disclose or suggest any specific enzyme and that the article vaguely refers to the role of biosynthetic enzymes and thus, "the publication does not disclose or suggest that a protein was isolated or characterized" and submit that the reference does not disclose or suggest the claimed invention. Applicant also argues that the reference evaluated the overall EPS biosynthetic enzyme activity by incubating cell preparations and in so doing the authors have not isolated or characterized the claimed protein and therefore applicant believes that the cited publication fails to anticipate or render obvious the claimed invention. Examiner respectfully disagrees with such an argument and asserts that such an argument is not persuasive to overcome the above rejection. The reference clearly identifies the strains of *Lactobacillus* that produce large amounts of exopolysaccharide. In addition, the reference also discloses the preparation of the enzyme composition. The reference clearly discloses EPS biosynthetic enzyme activity obtained from Lactobacillus strains as a dialyzable and soluble material obtained from the culture supernatants of the Lactobacillus. Therefore, while the study starts as enzyme localization studies, the authors end up with a preparation of the enzyme which had identical characteristics of that claimed in the instant claims. Therefore contrary to applicants arguments, the above reference clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Geel-Schutten et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703) as applied to claims 29-36, 38-44, 46-48 above, and further in view of the methods taught by Ausubel et al. (Short Protocols in Molecular Biology, 1997) regarding protein purification, sequencing and molecular cloning. Claims 37 and 45 are drawn to recombinant protein as claimed in claim 29, i.e., having glycosyltransferase activity and comprising an amino acid sequence that is at least 95% homology to amino acids 972-1781 of SEQ ID NO:2 or 95% amino acid homology to amino acids 531-1781 of SEQ ID NO:2. The reference of van Geel-Schutten as applied to claims 29 and 40 drawn to an isolated and purified glycosyltransferase isolated from *L.reuteri* has been discussed above.

With the enzyme preparations provided by van Geel-Schutten et al. it would have been obvious to one of ordinary skill in the art to make a recombinant enzyme of the same by further purifying the enzyme, microsequencing said purified protein, designing a probe based on the microsequencing data and analyzing a cDNA library of the lactic acid bacteria leading to the isolation of a cDNA clone and expressing such a clone to obtain a recombinant protein using the methods taught by Ausubel et al. Examiner would like to point out here that molecular cloning

has indeed become common knowledge in the art. There are innumerable books and manuals that teach said techniques. Commercial cloning kits specifically made for screening and isolating clones from bacterial, plant or animal sources are also available. One of ordinary skill in the art would be motivated to do so in order to make the enzyme in large quantities in view of its use for making glucans, which have great demand in the food industry. One of ordinary skill in the art would have a reasonable expectation of success since van Geel-Schutten et al. (a, b) teach enzyme preparation and the art or Ausubel et al. teach the methods for making recombinant proteins.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

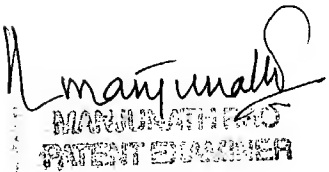
In response to the previous Office action, applicants have traversed the above rejection arguing that van Geel-Schutten reference fails to qualify as prior art. Applicant argues that the reference of van Geel-Schutten et al. (Appl. Microbiol. Biotechnol., 1998, Vol. 50:697-703) specifically does not disclose or suggest any information of the claimed protein and thus one of ordinary skill in the art would not be able to deduce whether a single enzyme or a complex of enzymes would be responsible for producing the polysaccharide. Applicant also argues that while Ausubel et al. teach methods, there is no suggestion to combine the above two references. Examiner respectfully disagrees with such an argument to be persuasive to overcome the above rejection. As explained above the reference of van Geel-Schutten et al. indeed is a prior art document which clearly teaches said enzyme preparation responsible for exopolysaccharide synthesis. While the reference may not teach a recombinant enzyme preparation and amino acid sequences of said enzyme, as explained above, it would have been quite obvious to those skilled

in the art to arrive at such inventions. Contrary to applicant's argument Ausubel et al. provide motivation to clone purified proteins and lists the advantages of making a recombinant protein from any purified enzyme or protein. The motivation to combine the above two references also generally comes from the art of molecular biology.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 6.30 a.m. to 3.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
April 7, 2004